Role of N-terminal pro-brain natriuretic peptide in detecting clinically significant cardiac involvement in systemic sclerosis patients

C. Chighizola[1], P.L. Meroni[1], B.E. Schreiber[2], J.G. Coghlan[2], C.P. Denton[2], V.H. Ong[2]

[1]University of Milan, IRCSS Istituto Auxologico Italiano, Milan, Italy; [2]Centre for Rheumatology and Connective Tissue Diseases, Royal Free Hospital, London, United Kingdom.

Cecilia Chighizola, MD
Pier Luigi Meroni, MD
Benjamin E. Schreiber, MD
John G. Coghlan, MD
Christopher P. Denton, PhD
Voon H. Ong, PhD

Please address correspondence to:
Dr Voon H. Ong,
Centre for Rheumatology and Connective Tissue Diseases,
UCL Medical School,
Royal Free Campus,
Rowland Hill Street,
London NW3 2PF, United Kingdom.
E-mail: v.ong@ucl.ac.uk

Received on November 22, 2011; accepted in revised form on May 2, 2012.

Clin Exp Rheumatol 2012; 30 (Suppl. 71): S81-S85.

Key words: systemic sclerosis, cardiac involvement, N-TproBNP

Competing interests: none declared.

ABSTRACT

Objectives. *Cardiac involvement is recognised as a poor prognostic factor among systemic sclerosis (SSc) patients, contributing significantly to mortality. We assessed the role of N-TproBNP in SSc-related cardiac involvement in a retrospective cohort of patients.*

Methods. *Serum N-TproBNP levels were measured in 21 SSc patients with clinically significant cardiac involvement and in a control group of 42 SSc patients without any evidence of heart involvement. All patients had normal pulmonary artery systolic pressure and none had serum creatinine above 140 micromol/L.*

Results. *Compared with those without cardiac involvement, N-TproBNP was significantly increased in SSc patients with heart involvement (median 11 and 219 pmol/L respectively, p<0.0001; CI 136-445). Receiver operating characteristic curves of N-TproBNP to predict the presence of cardiac involvement in SSc gave a sensitivity of 90.5% at a cut-off level of 50 pmol/L, with a specificity of 97.6%. By logistic regression analysis, N-TproBNP levels of 50 pmol/L were shown to be a strong predictor of heart involvement (OR 78, p<0.001, 95%CI 14-424). Moreover, a significant progressive reduction in N-Tpro BNP after initial presentation of cardiac involvement was observed in a subset of patients during 6 months of follow-up (p=0.023). Levels of N-TproBNP above the median value of 219 pmol/L did not predict survival (p=0.895, by log-rank). N-TproBNP levels strongly correlated negatively with LVEF (r=-0.7384, p=0.0002).*

Conclusions. *These data suggest N-TproBNP peptide may be a surrogate marker for cardiac involvement in SSc, selectively identifying patients with severe impairment of cardiac function.*

Introduction

Cardiac involvement is well recognised in systemic sclerosis (scleroderma, SSc) although often clinically occult. Its prevalence depends on the sensitivity of the diagnostic tools, ranging from 10 to 75% (1). Diffuse patients with rapid skin thickening are more prone to develop heart involvement (2). It usually occurs early, within 3 years from diagnosis (3). Scleroderma can involve myocardium, pericardium and the conduction system leading to a broad spectrum of clinical presentations (4). Myocardial fibrosis is the hallmark of SSc cardiac involvement. Heart involvement is recognised as a poor prognostic factor: the annual mortality rate attributable to cardiac disease is 1% (5). Therefore, early detection with non-invasive tools is critical. Annual echocardiography is recommended in SSc patients to screen for pulmonary arterial hypertension (PAH) (6). Cardiac MRI is increasingly recommended for accurate assessment of scleroderma myocardial involvement (7). However, it is expensive and not widely available; myocardial tissue biopsy is invasive and reserved for severe cases of indeterminate cause. Therefore, diagnostic screening tools are highly required.

Brain natriuretic peptide (BNP) is a neurohormone released from ventricular myocytes in response to increased myocardial pressure; it promotes vasodilatation and natriuresis (8). BNP is synthesised as a prohormone, proBNP. This precursor is cleaved to a biologically active peptide and an inactive fragment, the 76-residue N-TproBNP (9). BNP is rapidly metabolised while N-TproBNP is more stable overtime. Therefore, N-TproBNP is preferred as a potential biomarker. Multiple conditions affect N-TproBNP levels: age>65 years, gender and renal impairment (10).

Table I. Clinical characteristics of our SSc cohort.

Patient	Age	AutoAb	SSc Subset	mRSS	Severe ILD	SRC	Myo carditis	Arrythmia/ conduction disturbance	CAD	LVSD	Pericardial effusion	Cardiomyo-pathy	Cardiac MRI	PM/ ICD	Treatment	Basal NTpro BNP (pmol/L)	Follow-up NTpro BNP (pmol/L)
1	41	neg	dcSSc	15	X			X		X			X		CTX ev	502	390
2	66	ACA	lcSSc	6				X				X			C	41	18
3	41	aU3RNP	dcSSc	16			X	X			X		X		PDN + CTX	46	17
4	47	ATA	dcSSc/myositis overlap	20			X	X						X	IvIg + MMF	219	53
5	57	ATA	dcSSc	33	X		X	X				X	X		CTX	168	47
6	22	aU3RNP	dcSSc/myositis overlap	14				X			X				IvIg + CTX	28	n.a.
7	41	ATA	dcSSc	32	X					X	X (CT)				CTX	108	17
8	41	ATA	dcSSc/myositis overlap	2				X			X			X	AZA+IvIg+PDN	1017	140
9	62	aRNP	dcSSc/myositis overlap	4	X		X						X		C	91	41
10	53	aRNP	lcSSc	4	X			X	X	X				X	C	110	55
11	52	aSL	lcSSc	5		X		X		X				X	C	2200	n.a.
12	43	ATA	dcSSc	19						X					C	102	72
13	51	ACA	lcSSc	4						X	X				CTX+PDN+MMF	169	n.a.
14	54	aRNApol	dcSSc	6		X				X			X		C	8260	n.a.
15	50	ATA	dcSSc	32						X					MMF	334	n.a.
16	51	aU3RNP	dcSSc	n.a.		X		X		X	X				CTX	5076	8027
17	57	aU3RNP	dcSSc	n.a.			X			X			X	X	CTX	454	n.a.
18	70	aM2	lcSSc	4			X						X	X	C	736	n.a.
19	50	ANA +	lcSSc	6				X		X		X	X	X	C	695	57
20	61	ANA +	dcSSc	14	X			X						X	C	174	n.a.
21	42	neg	dcSSc	24				X		X			X	X	C	35	n.a.

Severe ILD: severe interstitial lung disease (FVC <70% predicted); SRC: scleroderma renal crisis; CAD: coronary artery disease; LVSD: left ventricular systolic dysfunction (LVEF < 0,40); cardiac MRI: cardiac magnetic resonance imaging; PM/ICD: pace-maker/intracardiac defibrillator; ACA: anti-centromere antibodies; ATA: anti-topoisomerase antibodies; aU3RNP: anti-U3RNP antibodies; aRNApol: anti-RNA polymerase antibodies; aSL: antibodies against SL; aM2: antibodies against M2; dcSSc: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; CT: cardiac tamponade; CTX: cyclophosphamide, C: cardiologic; PDN: prednisolone; Iv Ig: intravenous Immunoglobulins; MMF: mycophenolate mophetil; AZA: azathioprine; n.a.: not available.

The aim of this work was to retrospectively assess the role of N-TproBNP as a potential tool for the detection of SSc-related cardiac involvement.

Patients and methods

Twenty-one patients with SSc-related cardiac involvement were recruited from a single centre. Patients were categorised into limited (lcSSc) and diffuse cutaneous SSc (dcSSc) (11). Cardiac involvement was defined as haemodynamically significant arrhythmias, pericardial effusion or congestive heart failure. All patients were investigated with ECG and Echocardiogram. When appropriate, further investigations were undertaken.

All patients had normal pulmonary artery systolic pressure (sPAP<35 mmHg) with serum creatinine<140 micromol/L. Left ventricular systolic dysfunction (LVSD) was defined as a left ventricular ejection fraction (LVEF) <0.40, as determined by Echocardiogram.

This group of patients was compared with 42 unselected age-, sex- and disease subset-matched SSc patients without evidence of cardiac involvement or PAH and normal renal function.

Serum N-TproBNP was measured with Roche Modular Analytics E-170 immunoassay. Normal N-TproBNP levels were <20 pmol/L as recommended by the manufacturer. Clinical parameters for cardiac and lung function were contemporaneously assessed.

Mann-Whitney, Wilcoxon matched-pair and Kruskal-Wallis tests were used to compare N-TproBNP values between subgroups. Correlation between N-TproBNP and clinical variables was determined by Spearman's and Pearson's coefficients. Receiver operating characteristic (ROC) curve, logistic and linear regression analyses were performed. Univariate mortality analysis was performed with Kaplan-Meier method. Continuous variables were expressed as median values (interquartile range, IQR). Statistical analysis was performed using MINITAB 15 and STATA 11.

Results

In our cohort of patients with cardiac involvement, 14 subjects (66%) were female with a median age of 51 years (43-55). The median disease duration at the time of cardiac involvement was 40 months (14–70). 15 patients (71%) had dcSSc; 4 were diagnosed with myositis/dcSSc overlap syndrome (Table I).

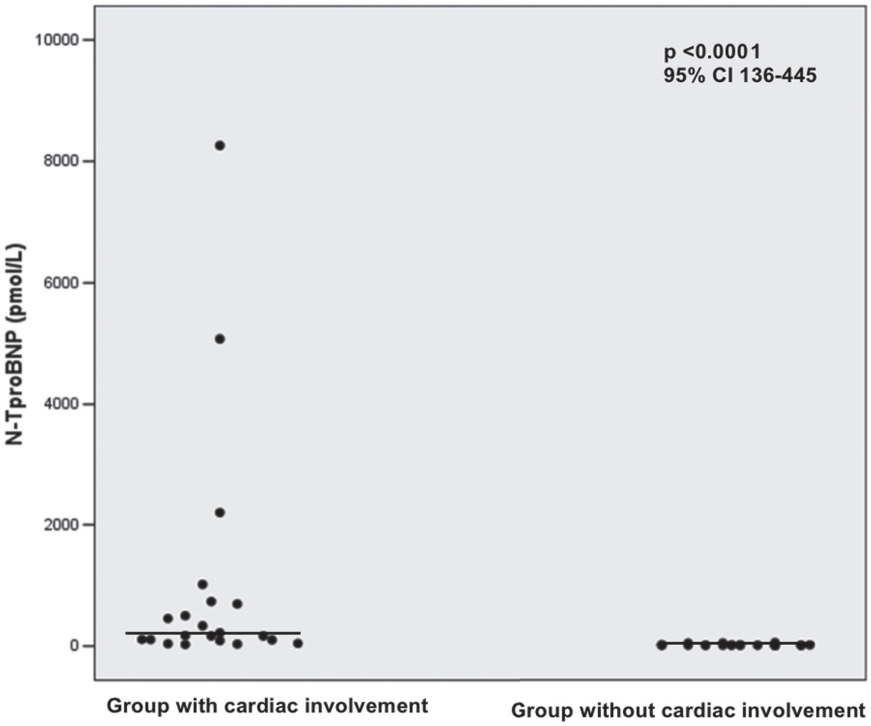

Fig. 1. Dot-plot of serum N-TproBNP levels in patients with cardiac involvement and controls. Median values for each subgroup are represented by horizontal bars. The median value is 219 pmol/L among patients with cardiac involvement, and 11 pmol/L among patients without.
95% CI=95% confidence interval.

N-TproBNP was significantly increased in SSc patients with cardiac involvement compared to those without (median 219 and 11 pmol/L respectively, p<0.0001; 95%CI 136–445, Fig. 1).

At logistic regression analysis, N-TproBNP levels>50 pmol/L were strongly predictive of heart involvement (OR 78, p<0.001, 95%CI 14-424).

Within the cardiac involvement group, N-TproBNP levels were significantly higher in patients with documented LSVD than in those with normal LVEF (median 598.5 and 105 pmol/L, respectively, p=0.0013, 95%CI 166–2109).

ROC-curves for N-TproBNP to predict cardiac involvement were drawn. At a cut-off level of 50 pmol/L, sensitivity was 90.5% and specificity 97.6% (95%CI 95–100), area under the curve was 0.99. The high specificity implied that the majority of patients with N-TproBNP below 50 pmol/L did not have cardiac involvement. This threshold level offers a negative predictive value (NPV) of 93.2% and a positive predictive value (PPV) of 94.7% in our cohort, where prevalence of cardiac involvement was 33%. Assuming the lowest estimated prevalence of cardiac involvement in SSc (10% (1)), serum N-TproBNP still remains a useful screening tool, with a PPV of 80% and a NPV of 98%.

To assess serial changes, thirteen patients had N-TproBNP levels repeated during a six-month follow-up, with a statistically significant reduction (p=0.023). Two patients experienced a relapse of cardiac disease and further N-TproBNP assessment were undertaken. We observed an increase in N-TproBNP levels, without attaining statistical significance (p=0.180).

Within the cardiac involvement group, high levels of N-TproBNP were defined as above the median value of 219 pmol/L. At this threshold value, there was no difference in survival between the two subgroups (p=0.895, by log-rank). Three deaths were recorded: all occurred within 36 months from onset of cardiac involvement. Two patients

with fatal outcome were in the high N-TproBNP subgroup.

As expected, a strong negative correlation was demonstrated between serum N-TproBNP and LVEF (r=-0.7384, p=0.0002). There was an inverse linear correlation of LVEF and log-transformed N-TproBNP values (r=-0.6921, Fig. 2). Linear regression analysis between N-TproBNP levels and LVEF indicated a trend towards statistical significance (p=0.066).

However, among those with cardiac involvement, there were no significant differences in N-TproBNP levels between genders, disease subsets and autoantibodies profiles. Similarly, there was no correlation between N-TproBNP and key clinical variables (age, mRSS, troponin-I, DL_{CO}, systolic and diastolic pressure). Moreover, N-TproBNP levels were not associated with digital ulceration, pulmonary fibrosis and myositis in this cohort.

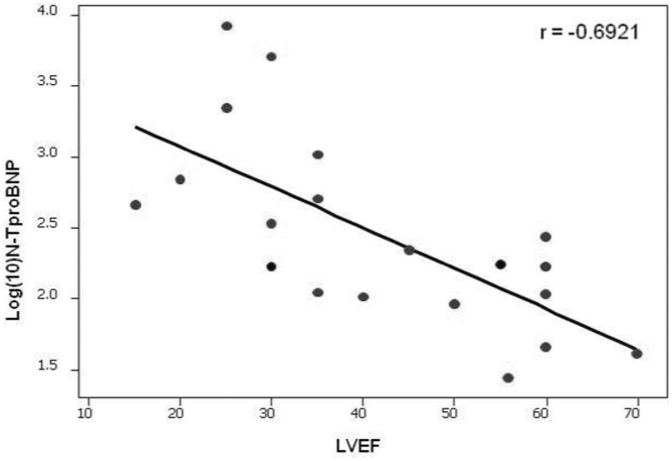

Fig. 2. Graph showing the correlation between log-transformed N-TproBNP levels and left ventricular ejection fraction (LVEF)

Discussion

In this retrospective study, we analysed serum N-TproBNP levels in a cohort of 21 SSc patients with clinically evident cardiac involvement. Interestingly, we showed a significant increase in N-TproBNP levels among patients with heart involvement compared to controls, suggesting that N-TproBNP may be a surrogate marker for cardiac involvement in SSc. Moreover, at logistic regression analysis N-TproBNP levels>50 pmol/L were strongly associated with heart involvement. Of note, at a cut-off level of 50 pmol/L, the PPV approached 95%, with a NPV well above 90%. These results have important clinical implications: N-TproBNP could be an effective tool to screen SSc patients for heart involvement. Patients with N-TproBNP levels>50 pmol/L should be referred for further cardiac assessment. Not surprisingly we found a significant correlation between N-TproBNP and LVEF; LVEF could also be predicted by N-TproBNP levels.

N-TproBNP has been previously investigated as a marker of cardiovascular status in SSc by Allanore and colleagues: however, they relied solely on echocardiograms to define cardiac involvement recruiting only patients with LVSD and increased sPAP (12). In this study, we enrolled patients with a wide array of SSc-related cardiac manifestations, ranging from LVSD, myocarditis to arrhythmias, conduction abnormalities and pericardial effusion. While N-TproBNP levels have been extensively investigated in SSc-related PAH and LVSD, its role in the spectrum of SSc cardiac disease has never been addressed (13). In our cohort, all patients with cardiac involvement including 9 patients with LVEF above 0.4 presented increased N-TproBNP levels: we therefore postulated fibrotic changes may lead to elevated N-TproBNP irrespective of the presenting cardiac manifestation. In support of this hypothesis, it has been recently demonstrated that BNP is synthetised also by cardiac fibroblasts; moreover, it has been shown to exert anti-fibrotic activities modulating collagen deposition (14, 15). Unfortunately, the limited number of patients in individual subsets precluded detailed examination. However, studies in the general population have shown that rhythm disturbances, pericardial disease and myocardial fibrosis are among the structural and functional cardiac abnormalities leading to release of natriuretic peptides (16). Similarly, it is tempting to postulate that an increase in N-TproBNP may herald a relapse of cardiac disease: however, few patients experienced clinical worsening preventing us to draw definitive conclusions.

This study presents several limitations. It's a retrospective study of patients with clinically evident cardiac involvement: this could have biased our cohort towards more severe disease. Another potential bias towards selection of patients with severely compromised cardiac function could be the low LVEF threshold set to define LVSD. Moreover, an increased sPAP was listed as an exclusion criterion: SSc cases with pulmonary hypertension secondary to cardiac involvement were excluded. Diastolic dysfunction has not been formally evaluated in this study: however, its prognostic significance is still unknown, with age-related changes not easily ascertained from pathological findings. The impact of age on N-TproBNP levels should also be considered. Given that cardiac involvement is a rather early complication in SSc disease course, our patients are relatively young compared to unselected SSc population: this could affect the diagnostic accuracy of the cut-off. Lastly, supportive therapies – notably ACE-inhibitors, angiotensin-receptor blockers, calcium-antagonists, diuretics – may also reduce N-TproBNP levels.

We believe this study may have clinically relevant implications. Cardiac involvement in SSc heralds a poor prognosis and diagnostic tools currently available are of invasive nature and not easily accessible. Our data support N-TproBNP as a simple yet reliable surrogate marker of a wide array of scleroderma-related cardiac manifestations: further studies are warranted to prospectively assess its diagnostic role. This work suggests N-TproBNP should be measured routinely in scleroderma patients; in those with increased levels, a comprehensive cardiac assessment should then be performed.

References

1. KAHAN A, ALLANORE Y: Primary myocardial involvement in systemic sclerosis. *Rheumatology* 2006; 45: 14-7.
2. PERERA A, FERTIG N, LUCAS M *et al*.: Clinical subsets, skin thickening progression rate, and serum antibody levels in systemic sclerosis with anti-topoisomerase I antibody. *Arthritis Rheum* 2007; 56: 2740-6.
3. MEUNE C, VIGNAUX O, KAHAN A, ALLANORE Y: Heart involvement in systemic sclerosis: evolving concept and diagnostic methodologies. *Arch Cardiovasc Dis* 2010; 103: 46-52.
4. CHAMPION HC: The heart in scleroderma. *Rheum Dis Clin North Am* 2008; 34: 181-8.
5. CZIRJÁK L, KUMÁNOVICS G, VARJÚ C *et al*.: Survival and causes of death in 366 hungarian patients with systemic sclerosis. *Ann Rheum Dis* 2008; 67: 59-63.
6. VACHIÉRY JL, COGHLAN G: Screening for pulmonary arterial hypertension in systemic sclerosis. *Eur Respir Rev* 2009; 18: 162-9.
7. HACHULLA AL, LAUNAY D, GAXOTTE V *et al*.: Cardiac magnetic resonance imaging in systemic sclerosis: a cross sectional observational study of 52 patients. *Ann Rheum Dis* 2009; 68: 1878-84.
8. WILKINS MR, REDONDO J, BROWN L: The natriuretic-peptide family. *Lancet* 1997; 349: 1307-10.
9. HALL C: Essential biochemistry and physiology of (NT-pro)BNP. *Eur J Heart Fail* 2004; 257-60.
10. WILLIAMS MH, HANDLER CE, AKRAM R *et al*.: Role of N-terminal brain natriuretic peptide (N-TproBNP) in scleroderma-associated pulmonary arterial hyperthension. *Eur Heart J* 2006; 27: 1485-94.
11. LEROY EC, BLACK C, FLEISCHMAJER R *et al*.: Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1998; 15: 202-5.
12. ALLANORE Y, WAHBI K, BORDERIE D *et al*.: N-terminal pro-brain natriuretic peptide in systemic sclerosis: a new cornerstone of cardiovascular assessment? *Ann Rheum Dis* 2009; 68: 1885-9.
13. ALLANORE Y, MEUNE C: N-terminal pro brain natriuretic peptide: the new cornerstone of cardiovascular assessment in systemic sclerosis. *Clin Exp Rheumatol* 2009; 27 (Suppl. 54): S59-63.
14. JARAI R, KAUN C, WEISS TW *et al*.: Human cardiac fibroblasts express B-type natriuretic peptide: fluvastatin ameliorates its up-regulation by interleukin-1alpha, tumour necrosis factor-alpha and transforming growth factor-beta. *J Cell Mol Med* 2009; 13: 4415-21.
15. HUNTLEY BK, ICHIKI T, SANGARALINGHAM SJ, CHEN HH, BURNETT JC: B-type natriuretic peptide and extracellular matrix protein interactions in human cardiac fibroblasts. *J Cell Physiol* 2010; 225: 251-5.
16. JANUZZI JL: The role of natriuretic peptide testing in guiding chronic heart failure management : Review of available data and recommendations for use. *Arch Cardiovasc Dis* 2012; 105: 40-50.